

is not less than 4.5 and not more than 7.0.

(viii) It passes the identity test.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, depressor substances, loss on drying, pH, and identity.

(ii) Samples required:

(a) If the batch is packaged for repackaging or for use in manufacturing another drug:

(1) For all tests except sterility: 10 packages, each containing approximately 500 milligrams.

(2) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(b) If the batch is packaged for dispensing:

(1) For all tests except sterility: A minimum of 12 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.106 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient sterile distilled water to give a stock solution of convenient concentration; and also, if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic syringe and needle, remove all of the withdrawable contents from each container represented as a single-dose container; or, if the labeling specifies the amount of potency in a given volume of the resultant preparation, withdraw an accurately measured representative portion from each container. Accurately dilute the sample thus obtained with sterile distilled water to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with sterile distilled water to the reference concentration of 30 micrograms of streptomycin per milliliter (estimated).

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 10 milligrams of streptomycin per milliliter.

(4) [Reserved]

(5) *Depressor substances.* Proceed as directed in § 436.35 of this chapter.

(6) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(7) *pH.* Proceed as directed in § 436.202 of this chapter, using a solution containing 200 milligrams per milliliter.

(8) *Identity*—(i) *Reagents.* (a) 10 percent ferric chloride stock solution: Dissolve 5 grams of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ in 50 milliliters of 0.1N HCl.

(b) 0.25 percent ferric chloride solution: Dilute 2.5 milliliters of 10 percent ferric chloride in 0.1N HCl to 100 milliliters with 0.01N HCl. Prepare the solution fresh daily.

(ii) *Procedure.* Using distilled water, dilute the sample to be tested to a concentration of approximately 1,000 micrograms per milliliter. To 5.0 milliliters of this solution, add 2.0 milliliters of 1N NaOH and heat in a boiling water bath for 10 minutes. Cool in the ice water for 3 minutes and then acidify the solution by adding 2.0 milliliters of 1.2N HCl. Add 5.0 milliliters of 0.25 percent ferric chloride reagent. A violet color indicates the presence of streptomycin.

[42 FR 21275, Apr. 26, 1977, as amended at 46 FR 60568, Dec. 11, 1981; 50 FR 19919, May 13, 1985]

§ 444.80 Tobramycin.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Tobramycin is 0-3-amino-3-deoxy- α -D-glucopyranosyl-(1 \rightarrow 4)-0-[2,6-diamino-2,3,6-trideoxy- α -D-ribohexopyranosyl-(1 \rightarrow 6)]-2-deoxy-L-streptomine. It is so purified and dried that:

(i) Its potency is not less than 900 micrograms of tobramycin per milligram on an anhydrous basis.

(ii) [Reserved]

(iii) Its moisture content is not more than 8 percent.

(iv) Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 9 and not more than 11.

(v) It gives a positive identity test for tobramycin.

(vi) Its residue on ignition is not more than 1.0 percent.

(vii) Its heavy metals content is not more than 30 parts per million.

(2) *Labeling*. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples*. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, identity, residue on ignition, and heavy metals.

(ii) Samples required: 10 packages, each containing approximately 500 milligrams.

(b) *Tests and methods of assay*—(1) *Potency*. Use either of the following methods; however, the results obtained from the microbiological turbidimetric assay shall be conclusive:

(i) *Microbiological turbidimetric assay*. Proceed as directed in § 436.106 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient distilled water to obtain a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with distilled water to the reference concentration of 2.5 micrograms of tobramycin per milliliter (estimated).

(ii) *Nonaqueous titration*. Proceed as directed in § 436.213 of this chapter, using the titration procedure described in paragraph (e)(2) of that section. Calculate the tobramycin content as follows:

Micrograms tobramycin per milligram =
$$\frac{[(A - B) \times (\text{normality of perchloric acid reagent}) \times 93.4 \times 100 \times 1,000]}{(\text{Weight of sample in milligrams} \times (100 - m))}$$

where:

A=Milliliters of perchloric acid reagent used in titrating the sample;

B=Milliliters of perchloric acid reagent used in titrating the blank;

m=Percent moisture of the sample.

(2) [Reserved]

(3) *Moisture*. Proceed as directed in § 436.201 of this chapter.

(4) *pH*. Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(5) *Identity*. Proceed as directed in § 436.318 of this chapter.

(6) *Residue on ignition*. Proceed as directed in § 436.207(a) of this chapter.

(7) *Heavy metals*. Proceed as directed in § 436.208 of this chapter.

[40 FR 57798, Dec. 12, 1975, as amended at 45 FR 16476, Mar. 14, 1980; 50 FR 19919, May 13, 1985]

§ 444.81a Sterile tobramycin sulfate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Sterile tobramycin sulfate is the sulfate salt of 0-3-amino-3-deoxy- α -D-glucopyranosyl-(1 \rightarrow 4)-0-[2,6-diamino-2,3,6-trideoxy- α -D-ribohexopyranosyl-(1 \rightarrow 6)]-2-deoxy-L-streptomine. It is a lyophilized powder. It is so purified and dried that:

(i) Its potency is not less than 634 micrograms and not more than 739 micrograms of tobramycin per milligram on an "as is" basis. If it is packaged for dispensing, its content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of tobramycin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not more than 2.0 percent.

(vi) Its pH in an aqueous solution containing 40 milligrams per milliliter, or when reconstituted as directed in the labeling, is not less than 6.0 and not more than 8.0.

(vii) It gives a positive identity test for tobramycin.

(viii) Its residue on ignition is not more than 1.0 percent.

(ix) Its heavy metals content is not more than 30 parts per million.

(2) *Labeling*. It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples*. In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, identity, residue on ignition, and heavy metals.

(ii) Samples required: